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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,608	01/06/2006	Hasan Kulaksiz	26605.00001	7597

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EXAMINER	
COUNTS, GARY W	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,608	KULAKSIZ ET AL.	
	Examiner	Art Unit	
	GARY W. COUNTS	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,15,16 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,15,16 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 9, 2009 has been entered.

2. Currently, claims 1, 3, 4, 15, 16, and 25-30 are pending and under examination.

Withdrawn Rejections

All rejections of claims not reiterated herein, have been withdrawn.

Specification

3. The disclosure is objected to because of the following informalities: The specification on page 1 should indicate the current status of all nonprovisional parent application references. For example, after the disclosure "is a Continuation-In-Part of Application No. 10/441,089 filed May 19, 2003". Applicant should insert --now U.S. Patent 7,320,894--. Also, after the disclosure "which is a Continuation-In-Part of Application No. 10/299,486 filed November 19, 2002". Applicant should insert --now U.S. Patent 7,411,048--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3, 4, 15, 16, and 25-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, in line 6 is indefinite in reciting improper Markush language in reciting, "the disease is selected from" because it appears to intend to limit the scope of the diseases recited in the claims but improperly defines it as such. Perhaps, Applicant intends, "the disease is selected from the group consisting on."

Claim 1, in line 11 is indefinite in reciting improper Markush language in reciting, "the tissue or fluid sample is selected from" because it appears to intend to limit the scope of the diseases recited in the claims but improperly defines it as such. Perhaps, Applicant intends, "the tissue or fluid sample is selected from the group consisting on."

Claim 1 is incomplete in reciting, "quantifying hecidin level in the sample", and "the non-physiological level of hepcidin is indicative of the disease" because it fails to clearly define what non-physiological level is expected to be obtained so as to be correlated to indication of a disease characterized by non-physiological levels as required by the preamble. A provision of 35 USC 112 second paragraph is for the specification to conclude with one or more claims particularly pointing out and clearly

and distinctly claiming the subject matter which the applicant regards as his invention. Such is not the case with claim 1. Although the claims are read in light of the specification, the specification can not be read into the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 4, 15, 16, and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification on page 4 discloses the C-terminus of hepcidin as being amino acids 65 to 84. The specification on page 6 discloses the C-terminal antibody EG(1)-HepC is raised against amino acids 70-84. Swinkels et al., (Clinical Chemistry 52, No. 6, 2006, pages 950-968) teaches that for hepcidin assays the development of reagents has been hampered by technical difficulties. Swinkels et al teaches that the development of immunochemical methods based on the production of specific anti-hepcidin antibodies is difficult because of the small size of hepcidin, that fact that the sequence is conserved among animal species, and the limited availability of antigen. Thus, at present only a limited number of tools are available to investigate human

hepcidin protein production, maturation and excretion (p. 961). Kemna et al., (Haematological 93(1), 2008, pgs 90-97) also teaches that immunochemical methods based on the use of specific anti-hepcidin antibodies are problematic mainly because of the limited availability of suitable antibodies (p. 93). Kemna et al teaches that this can be attributed to the small size of hepcidin, the compact and complex structure of the molecule, and the highly conserved sequence among species, complicating the elicitation of an immune response in host species (p. 93). The application does not disclose an antibody which specifically binds to any carboxy terminal portion of hepcidin in SEQ ID NO 2. The only C-terminal antibody of hepcidin disclosed in the specification is specific for epitopes within amino acids 70-84 of SEQ ID NO 2.

6. Claims 1, 3, 4, 15, 16, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification (e.g. p. 11, lines 25-27, pgs. 49-50) teaches and shows blood samples and ELISA assays using N-terminal antibodies to hepcidin to show a correlation with chronic renal insufficiency, renal anemia and hereditary hemochromatosis. The specification also provides that the C-terminal antibody EG(1)-HepC binds to hepcidin in western blot, immunochemistry and immunofluorescence assays(e.g. p. 6 and p. 55). However, the specification does not show that the

antibodies or fragments thereof bind or is reactive specifically to the carboxy terminal epitopes of SEQ ID NO: 2 that render it diagnostic for chronic renal insufficiency, renal anemia, and hereditary hemochromatosis. There is no description in the specification to show that the antibodies or fragments thereof bind or are specifically reactive to the carboxy terminal epitopes of SEQ ID NO: 2 to render rendering such epitopes as diagnostic for chronic renal insufficiency, renal anemia and hereditary hemochromatosis.

7. Claims 1, 3, 4, 15, 16 and 25-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting hepcidin with an antibody or fragment thereof that specifically binds to one or more epitopes of hepcidin located within amino acids 70-84 of SEQ ID NO 2, does not reasonably provide enablement for any and all carboxy terminal epitopes of SEQ ID NO 2 as broadly recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of

working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to obtaining a tissue or fluid sample from a subject and contacting the sample with an antibody or fragment thereof that specifically binds to one or more carboxy terminal epitopes of SEQ ID NO: 2: wherein the tissue or fluid sample is selected from kidney sample, a liver sample and a urine sample and detecting hepcidin the in sample.

The specification fails to teach a method of detecting hepcidin with an antibody which specifically binds to any carboxy terminal portion of hepcidin. The specification on page 4 discloses the C-terminus of hepcidin as being amino acids 65 to 84. The specification on page 6 discloses the C-terminal antibody EG(1)-HepC is raised against amino acids 70-84. Swinkels et al., (Clinical Chemistry 52, No. 6, 2006, pages 950-968) teaches that for hepcidin assays the development of reagents has been hampered by technical difficulties. Swinkels et al teaches that the development of immunochemical methods based on the production of specific anti-hepcidin antibodies is difficult because of the small size of hepcidin, that fact that the sequence is conserved among animal species, and the limited availability of antigen. Thus, at present only a limited number of tools are available to investigate human hepcidin protein production, maturation and excretion (p. 961). Kemna et al., (Haematological 93(1), 2008, pgs 90-97) also teaches that immunochemical methods based on the use of specific anti-hepcidin antibodies are problematic mainly because of the limited availability of suitable antibodies (p. 93). Kemna et al teaches that this can be attributed to the small size of hepcidin, the compact and complex structure of the molecule, and the highly conserved

sequence among species, complicating the elicitation of an immune response in host species (p. 93). Further, antibodies which specifically bind to the carboxy terminal epitope of hepcidin are not well known in the art and Swinkels et al and Kemna teach of the lack of such antibodies and the difficultly to make and obtain such antibodies. The only examples in the specification are directed to the use of the EG(1)-HepC antibody which is specific for epitopes within amino acids 70-84 of SEQ ID NO 2. At best determination of hepcidin can only be obtained with an antibody which specifically binds to one or more epitopes within amino acids 70-84 of SEQ ID NO 2. Therefore, such is not seen as sufficient to support the breadth of the claims and one skilled in the art cannot practice the claimed invention without undue experimentation, because one could not make an antibody which specifically binds to any portion of the C-terminal part of hepcidin molecule with a high level of predictability and without undue experimentation.

8. Claims 1, 3, 4, 15, 16, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining undue experimentation are set forth in *In re W*ands USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instant claims are directed to a method for diagnosing a disease characterized by non-physiological levels of hepcidin, comprising obtaining a tissue or fluid sample from a subject contacting the sample with an antibody or fragment thereof that specifically binds to one or more carboxy terminal epitopes of SEQ ID NO: 2, and quantifying hepcidin level in the sample; wherein: the disease is selected from chronic renal insufficiency, renal anemia and hereditary hemochromatosis; the tissue or fluid sample is selected from kidney samples, liver samples, and urine samples and the non-physiological level of hepcidin is indicative of the disease.

The specification fails to properly provide adequate written description to enable the methods as claimed. The specification on page 9 discloses that the physiological concentration of hepcidin in blood is in the range of about 50 to about 150 ng/ml and that nonphysiological concentrations are below or over this range. However, the specification does not provide physiological or non-physiological levels of hepcidin in urine, liver or kidney samples nor does the specification disclose a correlation of urine, liver or kidney sample levels with chronic renal insufficiency, renal anemia or hereditary hemochromatosis. There is no data or results provided which show a correlation of hepcidin obtained from a kidney sample, liver sample or urine sample wherein an antibody which specifically binds to one or more carboxy terminal epitopes of SEQ ID NO: 2 is used to detect hepcidin and used to diagnose chronic

renal insufficiency, renal anemia and hereditary hemochromatosis. Further, there is no evidence such as graphs or statistical values which provide a correlation of hepcidin levels compared to standards or controls. The only examples for detecting prohepcidin in human were directed to a sensitive ELISA which detected prohepcidin in serum of patients with hereditary hemochromatosis, chronic renal insufficiency and renal anemia (e.g. p. 11, lines 25-27, p. 49). However, the specification discloses that the C-terminal antibody EG(1)-HepC showed no immunoreactivity in this ELISA assay (e.g. p. 55). Thus, the specification only appears to provide significant results in serum using an antibody directed to N-terminal epitopes of hepcidin for diagnosing hereditary hemochromatosis, chronic renal insufficiency and renal anemia.

Also according to Strongin (Laboratory Diagnosis of Viral Infections, Sensitivity, Specificity, and Predictive Value of Diagnostic Tests: Definitions and Clinical Applications, Lennette, ed., Marcel Dekker, Inc., New York, pp.211-219, 1992) a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the following: (1) the sensitivity of the assay; (20 the true-positive test rate: (3) the false-negative test rate; (4) the specificity, or percentage of patients without the disease who will display a negative result; (5) the true-negative test rate; (6) the false-positive test rate; (7) the predictive value, or the probability that the test result is correctly indicating the presence or absence of the disease; (8) the prevalence, or number of patients in any given population that have the disease in question; (9) the efficiency or percentage of all results that are true; (10) the accuracy of the recited diagnostic assay.

Additional consideration must also be examined to enable the clinician to practice the invention, including assessment of the following: (1) when is the maximum sensitivity desired? (2) when is the maximum specificity desired?; (3) when is the maximum efficiency desired?; (4) how is the maximum sensitivity or specificity achieved?; (5) how is the predictive value maximized? An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test. Therefore, how can one of ordinary skill in the art positively diagnose chronic renal insufficiency, renal anemia and hereditary hemochromatosis using an antibody which specifically binds to one or more carboxy terminal epitopes of SEQ ID NO: 2 if one does not know what is a nonphysiological level or if a correlation exits between a level and chronic renal insufficiency, renal anemia and hereditary hemochromatosis. Further, if one does not know physiological levels how would one determine an increase or a decrease in level of if the increase or decrease would correlate with the disease. Thus the specification does not enable one skilled in the art to positively diagnose chronic renal insufficiency, renal anemia and hereditary hemochromatosis as claimed and one cannot practice the claimed method without undue experimentation.

Response to Arguments

9. Applicant's arguments filed April 9, 2009 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GARY W. COUNTS whose telephone number is (571)272-0817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ Gary W. Counts/
Examiner, Art Unit 1641

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

4/9/09